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NOTICE OF ALLOWANCE AND FEE(S) DUE

49443 7590 07/14/2008

Pearl Cohen Zedek Latzer, LLP
1500 Broadway
12th Floor
New York, NY 10036

EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/14/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,822	03/14/2005	Ehud Arbit	817.1009US	8526

TITLE OF INVENTION: ORAL INSULIN THERAPY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$300	$0	$1740	10/14/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

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10/500,822	03/14/2005	Ehud Arbit	817.1009US	8526

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nonprovisional	NO	$1440	$300	$0	$1740	10/14/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
BRADLEY, CHRISTINA	1654	514-004000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 344 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 344 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	10/500,822	ARBIT ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed on 5/30/2008*.

2. ☒ The allowed claim(s) is/are *59-83,85-105,108-117,119-129 and 131*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 6/19/2008
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Cecilia TSang/
Supervisory Patent Examiner
Art Unit 1654

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Morey Wildes on 6/20/2008.

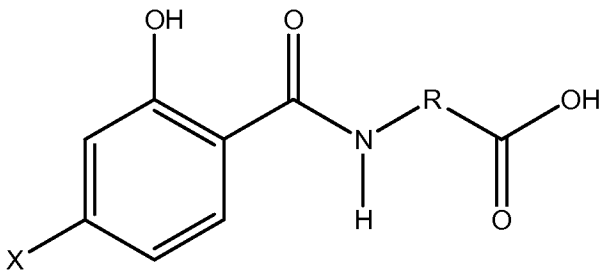
This listing of claims will replace all prior versions, and listings, of the claims in this application.

1-58. (Canceled)

59. A method of treating a human patient with diabetes mellitus, comprising orally administering to ~~said~~a human diabetic patient an oral dosage form comprising

a dose of unmodified insulin, and

an effective amount of a delivery agent of the formula or a pharmaceutically acceptable salt thereof:



,

wherein

i. X is hydrogen or halogen; and

ii. R is substituted or unsubstituted C1-C3 alkylene, substituted or unsubstituted C1-C3 alkenylene, substituted or unsubstituted C1-C3 alkyl (arylene), substituted or unsubstituted C1-C3 aryl (alkylene),

wherein said dosage form achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient as compared to an untreated diabetic patient.

60. The method of claim 59, wherein said oral dosage form ~~dose of unmodified insulin~~ achieves a ~~comparable~~ reduction in blood glucose concentration in human diabetic patients comparable~~d~~ to a subcutaneous insulin injection in those patients, while providing a lower plasma concentration of insulin in the peripheral circulation under acute, sub-acute or chronic conditions as compared to the peripheral plasma insulin concentration obtained via ~~the~~ subcutaneous insulin injection.

61. The method of claim 60, wherein said lower plasma insulin concentration is at least about 20%.

62. The method of claim 59, wherein said oral dosage form provides a ratio of portal vein to peripheral plasma insulin concentration from about 2.5:1 to about 6:1.

63. The method of claim 59, wherein said oral dosage form is solid.

64. The method of claim 59, wherein the oral dosage form provides a t_{max} for plasma insulin concentration at a time point from about 0.1 to about 1.5 hours after oral administration to said patients.

65. The method of claim 64, wherein at least about 80% of the blood glucose concentration reduction caused by said dose of insulin occurs within about 2 hours after oral administration of said oral dosage form.

66. The method of claim 59, wherein said oral dosage form upon pre-prandial oral administration to human diabetic patients causes the mean blood glucose concentration in said patients to be reduced for the first hour after oral administration relative to a mean baseline ~~(~~fasted~~)~~ blood glucose concentration in said patients.

67. The method of claim 59, wherein said oral dosage form upon pre-prandial oral administration provides a mean blood glucose concentration which does not vary by more than about 40% for the first hour after oral administration, relative to a mean baseline ~~(~~fasted~~)~~ blood glucose concentration in said patients, where a meal is eaten by said patients within about one half hour of oral administration of said dosage form.

68. The method of claim 59, wherein said oral dosage form upon pre-prandial oral administration provides a mean blood glucose concentration which does not vary by more than about 30% for the first hour after oral administration.

69. The method of claim 59, wherein said oral dosage form ~~dose of insulin~~ achieves a t_{max} for plasma insulin concentration at a time point from about 0.25 to about 1.5 hours after oral administration to a human diabetic patient, and upon preprandial administration to the patient provides effective control of blood glucose concentration in response to a meal as manifested by providing a blood glucose concentration which does not vary by more than about 40% for the first hour after oral administration from the baseline ~~(~~fasted~~)~~ blood glucose concentration in the

patient, and provides a return to baseline plasma insulin levels in the patient no later than 4 hours after oral administration.

70. The method of claim 69, wherein the insulin is a form of human regular insulin.

71. The method of claim 69, wherein the oral dosage form is solid.

72. The method of claim 59, wherein the oral dosage form is in the form of a tablet or capsule.

73. The method of claim 59, wherein the dose of unmodified insulin contained in the oral dosage form is from about 50 Units to about 600 Units ~~(from about 2 to about 23mg)~~.

74. The method of claim 59, wherein the dose of unmodified insulin contained in the oral dosage form is from about 100 Units ~~(3.8 mg)~~ to about 400 Units ~~(15.3 mg)~~.

75. The method of claim 59, wherein the dose of unmodified insulin is from about 150 Units ~~(5.75 mg)~~ to about 300 Units ~~(11.5 mg)~~.

76. The method of claim 59, which provides a t_{max} for plasma insulin concentration at about 0.1 to about 1.5 hours after oral administration.

77. The method of claim 59, which provides a t_{max} for plasma insulin concentration at about 0.25 to about 0.5 hours after oral administration.

78. The method of claim 59, wherein the oral dosage form begins delivering insulin into the portal circulation to achieve peak levels within about 30 minutes or less.

79. The method of claim 59, wherein said delivery agent is 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid.

80. The method of claim 59, wherein X is a halogen.

81. The method of claim 80, wherein said halogen is chlorine.

82. The method of claim 59, wherein R is C3 alkylene.

83. The method of claim 59, wherein said peak plasma delivery agent concentration occurs within two hours of oral administration.

84. (Canceled)

85. The method of claim 59, which provides a peak plasma delivery agent concentration that is from about 1,000 to about 100,000 ng/ml within about 0.1 to about 1.5 hours after oral administration.

86. The method of claim 59, which produces a maximal decrease in blood glucose in treated patients from about 0.1 to 1 hour post oral administration.

87. The method of claim 59, which produces a maximal decrease in blood glucose in treated patients at about 40 minutes post oral administration.

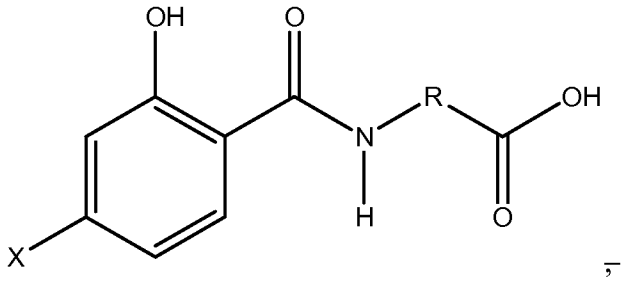
88. The method of claim 59, which produces a decreased blood glucose in fasted human patients by at least 10% within one hour post oral administration.

89. The method of claim 59, wherein said effective amount of ~~a~~the pharmaceutically acceptable delivery agent facilitates absorption of said insulin from the gastrointestinal tract of human diabetic patients~~, said oral dosage form being capable of being orally administered to a human diabetic patient to provide a therapeutic effect~~.

90. The method of claim 89, wherein the effective amount of said delivery agent is from about 1 mg to about 800 mg.

91. The method of claim 89, wherein the effective amount of said delivery agent is from about 100 mg to about 600 mg.

92. A method of treating impaired glucose tolerance, achieving glucose homeostasis, treating early-stage diabetes, or treating late-stage diabetes, comprising administering to a human patient in need thereof an oral dosage form comprising unmodified insulin and an effective amount of a delivery agent of the formula-or a pharmaceutically acceptable salt thereof,



wherein

i. X is hydrogen or halogen, and

ii. R is substituted or unsubstituted C1-C3 alkylene, substituted or unsubstituted C1-C3 alkenylene, substituted or unsubstituted C1-C3 alkyl (arylene), substituted or unsubstituted C1-C3 aryl (alkylene)

which oral dosage form achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient.

93. The method of claim 92, wherein the oral dosage form is administered on a chronic basis.

94. The method of claim 92, wherein the oral dosage form ~~unmodified insulin that~~ achieves a ~~comparable~~ reduction in blood glucose concentration in human diabetic patients comparable~~d~~ to a subcutaneous insulin injection in those patients, while providing a lower concentration of insulin in the peripheral blood circulation under acute, sub-acute or chronic conditions as compared to the peripheral plasma insulin concentration obtained via the subcutaneous injection.

95. The method of claim 92, wherein the oral dosage form ~~unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient and~~ provides a ratio of portal vein to peripheral plasma insulin concentration from about 2.5:1 to about 6:1.

96. The method of claim 92, ~~wherein the unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient,~~ wherein the dose of unmodified insulin is from about 100 Units ~~(3.8 mg)~~ to about 400 Units ~~(15.3 mg)~~ insulin.

97. The method of claim 92, wherein the oral dosage form ~~unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient and that~~ provides a t_{max} for plasma insulin concentration at about 0.1 to about 1.5 hours after oral administration.

98. The method of claim 92, wherein the oral dosage form ~~unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient and that~~ provides a t_{max} for plasma insulin concentration at about 0.25 to about 0.5 hours after oral administration.

99. The method of claim 92, wherein the oral dosage form ~~unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient, wherein the dosage form~~ begins delivering insulin into the portal circulation, ~~(~~via absorption through the mucosa of the stomach~~)~~, to achieve peak levels within about 30 minutes or less.

100. The method of claim 92, wherein said oral dosage form is solid.

101. The method of claim 100, wherein the ~~solid~~oral dosage form is in the form of a tablet or capsule.

102. The method of claim 92, wherein said delivery agent is 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid.

103. The oral solid dosage form of claim 92, wherein X is a halogen.

104. The method of claim 103, wherein said halogen is chlorine.

105. The method of claim 92, wherein R is C3 alkylene.

106. (cancelled)

107. (cancelled)

108. A method of treating a human diabetic patient, comprising orally administering an oral dosage form comprising an effective dose of insulin and a pharmaceutically acceptable delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid pre-prandially to a human diabetic patient, such that an insulin t_{max} at a time point from about 0.25 to about 1.5 hours after oral administration is attained and blood glucose concentration of the patient is effectively controlled in response to the meal as manifested by providing a blood glucose concentration which does not vary by more than about 40% for the first hour after oral administration from the baseline ~~(~~fasted~~)~~ blood glucose concentration in the patient, and which provides a return to baseline plasma insulin levels in the patient no later than 4 hours after oral administration.

109. The method of claim 108, wherein the insulin included in said oral dosage form is a human regular insulin.

110. A method of treating diabetics, comprising orally administering to diabetic patients on a chronic basis an oral insulin treatment comprising a dose of unmodified insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of the insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a peak blood plasma insulin concentration that is reduced relative to the peak blood plasma insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

111. The method of claim 110, wherein the <u>method provides a reduced</u> incidence of a disease state associated with chronic insulin administration ~~is reduced as a result of said chronic~~

~~administration~~ as compared to the incidence of a disease state associated with chronic insulin administration in a population of patients receiving subcutaneous injection of insulin.

112. The method of claim 110, wherein the method provides a reduced expression of genes associated with vascular disease as compared to the level of expression of genes associated with vascular disease resulting from an equivalent reduction in blood glucose concentration achieved in a population of patients via subcutaneous injection of insulin.

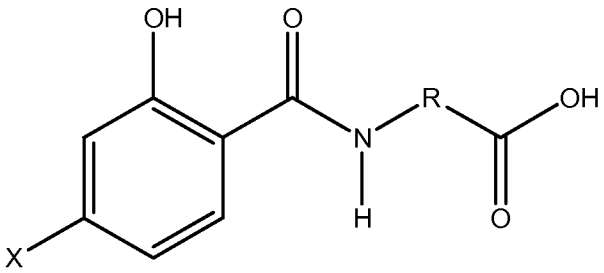
113. The method of claim 112, wherein the genes associated with vascular disease are selected from the group consisting of early response genes, genes associated with cytokines, genes associated with adhesion molecules, genes associated with lipid peroxidation, genes associated with thrombosis and combinations thereof.

114. The method of claim 113, wherein the early response genes are selected from the group consisting of c-myc, jun B, Egr-1, Ets-1 and combinations thereof.

115. The method of claim 110, wherein plasminogen activator inhibitor concentrations resulting from the method are lower as compared to the plasminogen activator inhibitor concentrations resulting from an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

116. The method of claim 110, wherein pro-inflammatory cytokine concentrations resulting from the method are lower as compared to the pro-inflammatory cytokine concentrations resulting from an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

117. A method of treating diabetics comprising orally administering to diabetic patients on a chronic basis an oral insulin treatment comprising a dose of unmodified insulin together with a delivery agent that facilitates the absorption of the insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a peak blood plasma insulin concentration that is reduced relative to the peak blood plasma insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin~~The method of claim 110~~, wherein the delivery agent ~~4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid~~ is a compound having the formula:



or a pharmaceutically acceptable salt thereof~~,~~ wherein

i. X is a halogen or hydrogen;

ii. R is substituted or unsubstituted C1-C12 alkylene, or ~~a~~ substituted or unsubstituted C1-C12 alkenylene.

118. (Cancelled)

119. The method of claims 110, wherein the insulin is selected from the group consisting of recombinant human insulin, bovine insulin, porcine insulin and functional equivalents thereof.

120. A method of treating diabetes and reducing the incidence and or severity of hyperinsulinemia associated with chronic dosing of insulin, comprising orally administering on a chronic basis to a diabetic patient a dose of insulin and a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of the dose of insulin from the gastrointestinal tract to provide therapeutically effective control and/or reduction in blood glucose concentrations, and a mean systemic plasma insulin concentration of the diabetic patient that is reduced relative to the mean systemic plasma insulin concentration provided by subcutaneous injection of insulin in an amount effective to achieve equivalent control and/or reduction in blood glucose concentration in a population of human diabetic patients.

121. A method of reducing the incidence and/or severity of one or more disease states associated with chronic administration of insulin, comprising treating diabetic patients via oral administration on a chronic basis with a therapeutically effective dose of a pharmaceutical composition which comprises insulin and a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of insulin from the gastrointestinal tract, such that the pharmaceutical composition provides a therapeutically effective reduction in blood glucose and a peak serum insulin concentration of the diabetic patient that is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

122. The method of claim 121, wherein the disease state is cardiovascular disease, and wherein the method provides a reduced expression of genes associated with vascular disease as compared

to the level of expression of genes associated with vascular disease resulting from an equivalent reduction in blood glucose concentration achieved in a population of patients via subcutaneous injection of insulin.

123. The method of claim 122, wherein the genes associated with vascular disease are selected from the group consisting of early response genes, genes associated with cytokines, genes associated with adhesion molecules, genes associated with lipid peroxidation, genes associated with thrombosis and combinations thereof.

124. The method of claim 123, wherein the early response genes are selected from the group consisting of c-myc, jun B, Egr-1, Ets-1 and combinations thereof.

125. The method of claim 121, wherein the disease state is selected from the group consisting of a neuropathy, a nephropathy, a retinopathy, an arteriopathy, atherosclerosis and combinations thereof.

126. The method of claim 121, wherein the disease state is selected from the group consisting of coronary artery disease, hypertensive cardiomyopathy and congestive heart failure.

127. The method of claim 110, wherein said disease state is vascular diseases.

128. A method of treating diabetes and reducing the incidence and or severity of hyperinsulinemia associated with chronic dosing of insulin, comprising orally administering on a chronic basis to a diabetic patient a dose of insulin and a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid that facilitates the absorption of the dose of insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a

peak serum insulin concentration of the diabetic patient that is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

129. A method of reducing the exposure of the vasculature of diabetic patients to hyperinsulinemic conditions, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of insulin treatment is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

130. (cancelled)

131. A method of treating diabetic patients, comprising orally administering an oral insulin ~~treatment~~formulation comprising a dose of insulin together with a delivery agent 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a ~~desired~~effective amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of said oral insulin treatment is not substantially greater than normal physiological levels.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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